PATENT #16
Docket No. 204372000301

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Marian Christopher

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Lynn E. SPITLER
and Anthony E. Maida III

Serial No.: 09/300978

Filing Date: 28 April 1999

For: METHODS OF ELICITING AN ANTITUMOR IMMUNE RESPONSE TO PROSTATE TUMORS (as amended)

Examiner: Phillip Gambel, Ph.D.

Group Art Unit: 1644

BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Appellants hereby appeal from the final rejection of claims 13-24 mailed 27 June 2001. A Notice of Appeal was filed 18 September 2001. A Petition for an Extension of Time for filing the Brief of one month to extend the time for response to 18 December 2001 is attached hereto along with the required fee. Appellants respectfully request that the rejections be reversed. In accordance with 37 C.F.R. § 1.192, this Brief is filed in triplicate and is accompanied by the required fee.

sd-70995

I. Real Party in Interest

The present application is assigned to Jenner Technologies, a California corporation.

II. Related Appeals and Interferences

Appellants are aware of another appeal with respect to the grandparent application of the present application, US Ser. No. 08/105,444 filed August 11, 1993, which may have a bearing on the Board's decision in the pending Appeal.

III. Status of claims

The application was filed with claims 1-12. All of these claims have been cancelled by the preliminary amendment filed 28 April 1999. Claims 13-24 have been added in that same preliminary amendment. Upon filing of this appeal, the amendment filed 15 August 2001 has been entered which amends claim 13 and cancels claims 14 and 17, according to the Advisory Action mailed 18 September 2001. These claims are rejected.

IV. Status of Amendments

In response to a final rejection herein, appellants submitted an Amendment filed 15 August 2001 amending claim 13 and a canceling claims 14 and 17 as described above. According to the Advisory Action mailed 18 September 2001, this amendment was to be entered upon filing an appeal. Appellants also submit herewith a Second Amendment in response to final rejection, a copy of which is attached. In this Second Amendment, claims 15, 16, 18, and 19 have been amended to correct the antecedent basis with respect to claim 13, and claim 13 has been further amended to simplify the claim language. This amendment has not been entered as of the filing of this appeal brief.

V. Summary of the Invention

Prior art formulations for vaccines designed to produce an antitumor response from an immune system have been based on the use of antigens that are uniquely associated with the tumors *per se*. The present invention represents a different approach in that, rather than such uniquely tumor-associated antigens as active ingredients, the present invention employs antigens, namely PSMA and PAP, that are associated with the host prostate tissue -- that is, the antigens are found in the prostate in contrast to other tissues. Generally, these antigens are found both in the normal prostate and in malignant prostate tissue. (See page 4, lines 11-22.) The invention takes advantage of the fact that the prostate is not an essential organ and thus an immune response which could include disruption of normal tissue is acceptable. See page 4, lines 11-22.

The PAP or PSMA antigen is specifically associated with prostate, whether normal or malignant. The antigen can be supplied, for example, as the antigen *per se* or as an expression system which is able to produce the protein or peptide *in situ* in the subject. The invention is directed to methods of use. (See the paragraph bridging pages 4 and 5.)

Thus, the invention described in claims 13, 15-16, 18-24 is directed to methods of eliciting an antitumor immune response to prostate tumors using PSMA and/or PAP, or a nucleic acid that generates either antigen as an active ingredient. Claims 20-23 are directed to the same method where either the antigen is further encapsulated in a liposome or coupled to a liposome and/or the liposome contains an adjuvant. The method of claim 24 further defines the method as being directed to a subject afflicted with prostate cancer and/or wherein the subject has been surgically treated to excise the tumor but is at risk for recurrence.

VI. Issues

The following issues are presented for review.

1. Whether structures of nucleotide sequences encoding PSMA and PAP that are known in the art must be provided in the specification if the specification as filed includes reference to such prior knowledge. This issue is reflected in a rejection under 35 U.S.C. § 112, first paragraph (written description).

2. Whether the language in claim 12 of the originally filed application provides written description basis for the same language as used in new claim 24. This issue is reflected in an additional rejection under 35 U.S.C. § 112, first paragraph (written description).

3. Whether the cited Spitler *et at.* (U.S. Pat. No. 5,738,867) and Israeli *et at.* (U.S. Pat. No. 5,538,866) references can be used to render the present claims obvious under 35 U.S.C. § 103 and concomitantly ignored for purposes of enablement under 35 U.S.C. § 112, first paragraph. This issue is reflected in the "squeeze" rejection under both 35 U.S.C. § 103 and 35 U.S.C. § 112, first paragraph (enablement).

4. Whether there is enabling disclosure for "over-represented prostate specific antigen" in claims that define the "over-represented prostate specify antigen" as limited to PSMA or PAP (or mixtures) in view of the Office's statement that PSMA and PAP are properly enabled.

5. Whether the claimed methods are obvious under 35 U.S.C. § 103 over the combination of Spitler *et at.* (U.S. Pat. No. 5,738,867) in view of Israeli *et at.* (U.S. Pat. No. 5,538,866) and the present disclosure where neither Spitler nor Israeli nor the acknowledged art in the present specification suggests that a normal tissue antigen shared by a tumor be used to elicit an active tumor response.

VII. Grouping of Claims

The inventive concept of all claims is the same and all claims may be considered together for purposes of the rejection under 35 U.S.C. § 103.

However, it should be evident that the rejection under 35 U.S.C. § 112, as set forth in issue No. 1 above, is inapplicable to claims 15-16, which are limited to the two specific known antigens: prostate-specific membrane antigen (PSMA) or prostatic acid phosphatase (PAP).

VIII. Argument

It is believed that issues 1-5 should be resolved in favor of appellants for the following reasons:

A. The structures of nucleotide sequences encoding PSMA and PAP are known in the art and sufficiently show inventor was in possession of claimed method of using such nucleotide sequences.

A *prima facie* case of lack of written description under 35 U.S.C. § 112, first paragraph has not been established. A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. The Examiner has the initial burden of presenting by a preponderance of evidence why a person of ordinary skill in the art would not recognize in an appellant's disclosure a description of the invention defined by the claims. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.

Appellant asserts that a person of ordinary skill in the art would recognize a description in the specification of the invention defined by the claims. With respect to "over-represented antigens," the claims are limited to PSMA, PAP, or nucleotide sequences encoding them *per se*. Support for PSMA and PAP and the nucleotide sequences encoding them is found in the present specification on page 9, lines 9-27 (PSMA), and page 7, line 21 to page 8, line 5 (PAP). The specification provides methods for preparing the antigens on page 10, line 9 to page 12, line 2. Hence, the specification sufficiently describes the specific "over-expressed antigens" enumerated in claim 13.

With respect to the term "nucleic acid sequences," claim 13 includes nucleic acid sequences encoding PSMA or PAP *per se*. The structure of these proteins and of the nucleic acids encoding them is known in the art. See page 8 of the specification, lines 1-5 (PAP) and page 9 of the specification, lines 9-11 (PSMA). The specification further describes the nucleic

acids of claim 13 on page 6, line 21 to page 7, line 14. In addition, the specification on page 16, line 24 to page 17, line 4, describes how DNA encoding polypeptides such as PAP, PSMA, or portions of these may be administered to a subject by way of a viral expression vector. Hence, the specification demonstrates that Applicant plainly had possession of "nucleic acid sequences" as set forth in claim 13.

Therefore, the specification provides an adequate written description for the terms "over-represented antigens" and "nucleic acid sequences."

Nonetheless, to simplify the claim language, in the Second Amendment in response to the Final Office Action filed on the same date as herewith, appellants have removed the reference to "at least one over-represented antigen" in claim 13, as this language was redundant due to the fact that PSMA and PAP specifically are defined in claim 13 as the over-represented antigens. In addition, the Second Amendment further amended claim 13 to include a specific reference to PSMA or PAP as those antigens which are generated by the nucleic acids. These amendments do not affect the scope of the claims, but merely clarify the claim language. There should be no question now that the scope of the present claims are directed to PSMA, PAP and nucleotides encoding them.

Moreover, claims 15-16 are not rejected for improper written description. Thus, it is evident that claims 15-16, which are directed to the PSMA (claim 15) or PAP (claim 16) antigen, properly conform to the written description requirement although no polypeptide sequence has been recited in the specification. Similarly, although the nucleotide sequences encoding PSMA or PAP specifically have not been recited in the specification, these nucleotide sequences are known in the art and likewise properly conform to the written description requirement. Thus, the rejection for lack of written description may be withdrawn.

B. The subject matter of claim 24 represents subject matter originally claimed in the application as filed (claim 12).

A *prima facie* case of lack of written description under 35 U.S.C. § 112, first paragraph has not been established with respect to claim 24. As discussed above, a description as filed is presumed to be adequate.

The subject matter of claim 24 represents subject matter originally claimed in the application as filed (claim 12). Original claim 12 required that the subject be

(a) afflicted with metastatic prostate cancer; and/or

(b) been surgically treated to excise the tumor but is at risk for recurrence (with the optional limitation that the subject is in a "neoadjuvant" setting) or

(c) wherein the subject is a potential prostate tumor-bearing subject.

The changes simply delete the last alternative (c) and the optional limitation to the second (b). Thus, the subject matter is completely disclosed *in haec verba* in the application as originally filed. No reasoning has been set forth by the Examiner that would show that a skilled artisan would not recognize that the inventors had possession of the claimed invention. Accordingly, this basis for rejection may properly be withdrawn.

C. The squeeze rejection under 35 U.S.C. § 103 and 35 U.S.C. § 112, first paragraph (enablement) is improper as the references cannot be used to render obvious the claimed invention while being ignored to render the present claims not enabled under 35 U.S.C. § 112, first paragraph.

If the enablement rejection is not overcome by the amendment to claim 13 in the Second Amendment in response to final rejection, a copy of which is attached herewith, or this amendment is not entered, the rejection under 35 U.S.C. § 112, first paragraph (enablement) should not stand because an improper "squeeze" rejection has been made. The Office argues both that a) a skilled person would not be enabled at the time the application was filed to use PSMA and PAP, i.e. the "over-represented prostate specific antigens" in the methods of the

invention under 35 U.S.C. § 112, first paragraph (enablement), and b) the art references were sufficiently enabled to teach a skilled person to use PSMA and PAP according to the methods of the invention under 35 U.S.C. § 103. Such rejections used concomitantly are inconsistent. Accordingly, this basis for the enablement rejection may properly be withdrawn.

D. The Office agrees that the "over-represented prostate specific antigens" in the claims, namely PSMA and PAP are enabled by the specification

The Examiner acknowledges in the final Office action that the present specification is enabling for "full length ...PSMA and PAP," however, not for "over-represented prostate specific antigens." As described above in section "A", the claims are limited to PSMA, PAP, or nucleotide sequences encoding them *per se*. Thus, the claims are enabled for the specific "over-represented prostate specific antigens" defined in the claims, namely PSMA and PAP. Nonetheless, in the Second Amendment in response to final rejection, appellants have removed the language directed to "over-represented prostate specific antigens," without altering the scope of the claims to simplify this issue for the Office and for the appeal.

Thus, the rejection under 35 U.S.C. § 112, first paragraph (enablement) may be properly withdrawn.

It is believed that the rejection under 35 U.S.C. § 112, first paragraph (enablement) has been overcome with respect to the language relating to "immunologically effective portion thereof." This language was deleted in the First Amendment in response to final rejection, which is referenced by the Advisory Action that states that the rejection over "immunologically reactive/effective portion" has been overcome. Although no rejection in the Advisory Action was specified, it is believed that the rejection in question is 35 U.S.C. § 112, first paragraph (enablement), and thus it is believed that there is no issue on appeal with respect to this portion of the rejection.

E. The prior art references cited, taken individually or together, fail to suggest the present invention.

As a preliminary matter, if the enablement rejection in section "E." stands, then the obviousness rejection under 35 U.S.C. §103 should be withdrawn on the basis of the arguments presented in section "C". However, assuming that the enablement rejection is withdrawn, the present invention is not rendered obvious by Spitler in combination with Israeli and in view of the art acknowledged methods of delivering antigens of interest to stimulate antitumor responses as disclosed on pages 10-19 of the instant specification, as asserted by the Office.

The Office has not established a *prima facie* case of obviousness. According to Section 2143 of the MPEP, a *prima facie* case of obviousness is presented if three requirements are met. First, there must be a suggestion or motivation, either in the references themselves or in the knowledge in the art, to modify the reference or to combine teachings. Second there must be a reasonable expectation of success. Third, the prior art reference must teach or suggest all the claim limitations.

The basis for the rejection appears to reside in the general involvement of antigens characteristic of the prostate in treatment of prostate cancer. The rejection fails to recognize how different the claimed approach is from that taught by the references. The difference can be succinctly stated once again: (a) An antigen shared by the normal cells of the prostate with prostate tumors (i.e., that are not unique to the tumor) is used to elicit an active immune response against the tumor, and (b) the antigen is not used as a target for an antibody or immunoconjugate. Appellants are unable to find any suggestion in this combination of references that a normal tissue antigen shared by the tumor should be used to elicit an active tumor response. The Examiner has been unable to point to any such suggestion.

Appellants certainly recognize that it is the combination of references that has been applied not the references individually; however, it will be helpful to summarize the teachings of each reference.

The primary reference, Spitler, refers to the use of a tumor associated antigen which is not found in normal tissue as the active ingredient in a vaccine. The whole concept of the present invention resides in using, instead of such an obvious target, an antigen that occurs in normal tissue.

Israeli discusses the isolation of nucleic acid encoding PSMA. Also, Israeli discusses *ex vivo* production of antibodies against PSMA and does not suggest eliciting an immune response in a subject. Therefore, Israeli does not cure the defects of Spitler because it also fails to suggest a method for eliciting an immune response in a subject using an antigen that occurs in normal tissue.

The documents cited in the specification on pages 10-19 discuss general methods of delivering antigens of interest to stimulate antitumor responses. However, none of these documents cure the defects of Spitler and Israeli because they fail to discuss methods for eliciting an immune response in a subject using an antigen that occurs in normal tissue.

Eliciting an immune response in a subject using an antigen that occurs in normal tissue is nowhere suggested in the cited art. Thus the third requirement described above for establishing a *prima facie* case of obviousness has not been established, since the references do not teach or suggest all of the claim limitations.

Even if the cited documents resulted in the claimed subject matter, which they do not, there is no motivation to combine the documents. The Court of Appeals for the Federal Circuit has stated that there are three possible sources for a motivation to combine documents: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *In re Rouffet*, 47 USPQ.2d 1453 (Fed. Cir. 1998).

The asserted motivation for combining the documents ignores the fact that PSMA is not a tumor-associated antigen not associated with normal tissue. Thus, the disclosure of Spitler where an antigen uniquely associated with the tumor and not expressed in normal tissue and thus foreign to the host is used as an active ingredient in a vaccine provides no incentive (absent the invention) to combine its teachings with a document which teaches a normally produced antigen. Thus, the first requirement described above for establishing a *prima facie* case of obviousness has not been established because there is no motivation to modify or combine references.

For this reason, the rejection over Spitler in combination with Israeli in view of the present disclosure may properly be withdrawn.

IX. Appendix

Attached hereto is Appendix A containing a copy of the claims involved in the Appeal. Appendix B is a copy of a Second Amendment in response to the final rejection filed on the same date as herewith.

Conclusion

For the reasons stated above, appellants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph for asserted lack of written description and enablement as well as that over the art be reversed and claims 13, 15, 16 and 18-24 be passed to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 204372000301. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: December 18, 2001 By: _____

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APPENDIX A

Currently Pending Claims

13. A method to elicit an antitumor immune response to prostate tumors in a subject, which method comprises

administering to said subject at least one active ingredient formulated for administration to said subject,

wherein said active ingredient comprises or expresses at least one antigen over-represented in the prostate gland,

wherein said active ingredient is human prostate-specific membrane antigen (PSMA); or prostatic acid phosphatase (PAP); or mixtures of the foregoing; or

is a nucleic acid that generates said antigen or antigens *in situ*.

15. The method of claim 13 wherein said active ingredient is human PSMA or said portion thereof.

16. The method of claim 13 wherein said active ingredient is PAP or said portion thereof.

18. The method of claim 13 wherein said active ingredient is a nucleic acid that generates PSMA or said portion thereof *in situ*.

19. The method of claim 13 wherein said active ingredient is a nucleic acid that generates said PAP or said portion thereof *in situ*.

20. The method of claim 13 wherein the active ingredient is encapsulated in liposomes and/or coupled to liposomes.

21. The method of claim 20 wherein said liposomes contain an adjuvant.

22. The method of claim 13 which further includes at least one adjuvant that enhances the antitumor immune response.

23. The method of claim 22 wherein said adjuvant is selected from the group consisting of Freund's complete adjuvant; alum; lipid A; monophosphoryl lipid A; *Bacillus Calmette-Guerin* (BCG) or other bacteria polysaccharides; saponins; detoxified endotoxin (DETOX); muramyl tripeptide or muramyl dipeptide or their derivatives; SAF1; lymphokines; cytokines; colony stimulating factors; nonionic block copolymers; and immune stimulating complexes (ISCOMS).

24. The method of claim 13 wherein said subject is afflicted with metastatic prostate cancer; and/or wherein said subject has been surgically treated to excise said tumor but is at risk for recurrence.